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CLINICAL APPLICATION

Treatment of Diabetes Prior to and after Bariatric Surgery

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Abstract

The number of patients undergoing bariatric surgery for morbid obesity is increasing. Type 2 diabetes is common among patients undergoing bariatric surgery. The effect of bariatric surgery on glycemia is profound in patients with diabetes and might vary between different bariatric surgical procedures. Therefore, almost invariably, there is a need to adjust antidiabetic drug dosages in the postoperative period in order to prevent hypoglycemia.

Moreover, preoperatively, very low calorie diet protocols are applied in many centers to facilitate surgery by reducing liver volume. Because low caloric intake will increase insulin sensitivity, there is also a need for dose adjustments of glucose-lowering drugs during this period as well. Guidelines for adjustments of antidiabetic treatment before and after bariatric surgery are scarce. In this article, an overview of different bariatric surgical procedures as well as their effects on diabetes are presented. Recommendations on the perioperative antidiabetic treatment are proposed.

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Introduction

Type 2 diabetes (T2DM) is a major health problem with increasing incidence in the Western world as well as in developing countries. The disease is chronic and the treatment involves lifestyle changes, oral antidiabetic drugs, and/or injections of insulin or glucagon-like peptide-1 (GLP-1) analogs as well as treatment for any ongoing hypertension and/or hyperlipidemia. Although the mortality from cardiovascular disease in diabetes seems to decline over time, it is still at least double compared to that in a nondiabetic population.[1] Diabetes is associated with obesity; the more obesity, the greater the risk for T2DM. Current recommendations for bariatric surgery are based on body mass index [(BMI), body weight (kg)/length (m^2)]. Body mass index >25 is classified as overweight, and BMI >30 is classified as obesity. Similar to diabetes, obesity is also associated with increased risk of morbidity and mortality. The total risk of premature death has been reported to be increased at least two-fold in patients with obesity compared with normal-weight subjects.[2] Moreover, the risk of death from cardiovascular disease has been reported to be increased three- and five-fold in obese women and

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Abbreviations: (BMI) body mass index, (BPD) bilopancreatic diversion, (BPD-DS) bilopancreatic diversion with duodenal switch, (GLP-1) glucagon-like peptide-1, (HbA1c) hemoglobin A1c, (NPH) neutral protamine Hagedorn, (RYGB) roux-en-Y gastric bypass, (SOS-study) Swedish Obese Subjects Study, (T2DM) type 2 diabetes, (VLCD) very low calorie diet

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men, respectively, and there is an increased risk for several types of cancer.[3] Treatment modalities for obesity include lifestyle changes, diet regimens, pharmacological treatment, and bariatric surgery. Of these, surgery is the most efficient alternative and has been demonstrated to be associated with maintained weight reduction as well as with effects on obesity-associated conditions such as T2DM. Today, the most commonly used limits to qualify for bariatric (weight-reducing) surgery in Europe as well as in the United States are a BMI of 35 with comorbidity and 40 without comorbidity, such as T2DM. In the large Swedish Obese Subjects Study (SOS-study), in which over 4000 patients who were treated with surgery or traditional treatment for obesity within primary care were studied, data were presented demonstrating a substantial reduction in mortality in patients undergoing surgery.[4] The demand for bariatric surgical procedures for morbid obesity has increased substantially between 2008 and 2010, during which the annual procedures performed in Sweden increased from 2800 to 8000.

Among patients undergoing bariatric surgery for morbid obesity, 10–28% have T2DM. Moreover, an additional 10–30% display reduced glucose tolerance and/or increased fasting glycemia.[5] Apart from weight reduction, one of the most prominent effects of bariatric surgery is a dramatic improvement of any preexisting diabetes. Thus, in the SOS-study, total resolution from diabetes, defined as fasting P-glucose <6.1 mmol/liter without the use of glucose-lowering medication, was reported in 72% of the patients after 2 years. Moreover, during the same time, the number of patients with newly diagnosed diabetes during follow-up was only 1% and 7%, respectively, after 2 and 10 years. Corresponding results for the conventionally treated group was 8% and 24%.[6] Due to these marked effects by bariatric surgery on T2DM, it has been suggested that obese patients with T2DM and a BMI lower than 35 should also be considered for bariatric surgery. In a review, it was found that surgical treatment effectively ameliorates and even resolves diabetes also at a lower BMI, but it was also stated that there is a need for randomized trials with extended follow-up to clearly define benefits and drawbacks.[7] However, as bariatric surgery is shown to be a potent approach to improve metabolic control in patients with T2DM, there will be an obvious need for adjustment of antidiabetic treatment in the perioperative phase of surgery. We will hereby present an overview of common bariatric surgical techniques and the possible mechanisms behind their metabolic effects. Furthermore, a proposed scheme for adjustment of glucose-lowering drugs is presented.

Bariatric Surgical Procedures

Traditionally, bariatric surgical procedures are classified as restrictive, malabsorptive, or combined. In restrictive procedures, weight loss is achieved solely by reduced capacity for nutritional intake, whereas in malabsorptive procedures, the effect is induced through bypass of absorptive and secretory areas of the stomach and small intestine. According to this classification, vertical banded gastroplasty (**Figure 1**), adjustable gastric banding (**Figure 2**), and sleeve gastrectomy (**Figure 3**) are purely restrictive procedures, whereas bilopancreatic diversion [(BPD), **Figure 4**] and bilopancreatic diversion with duodenal switch [(BPD-DS), **Figure 5**] are malabsorptive. In roux-en-Y gastric bypass [(RYGB), **Figure 6**], a small gastric pouch is connected to the small intestine through a gastroenteroanastomosis. The biliopancreatic limb (the major disconnected part of the stomach, duodenum, and proximal small intestine) is connected via an enteroanastomosis to the alimentary limb 120–150 cm below the gastric pouch. By this means, RYGB combines restriction of food intake with reduction

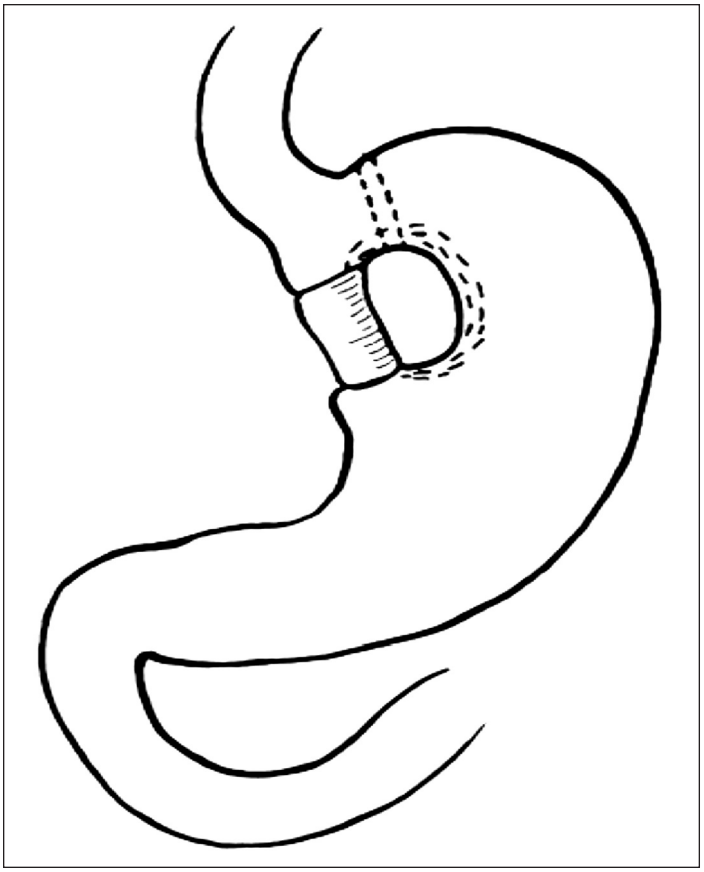

Figure 1. Vertical banded gastroplasty. Adapted with permission from e-SPEN.[8]

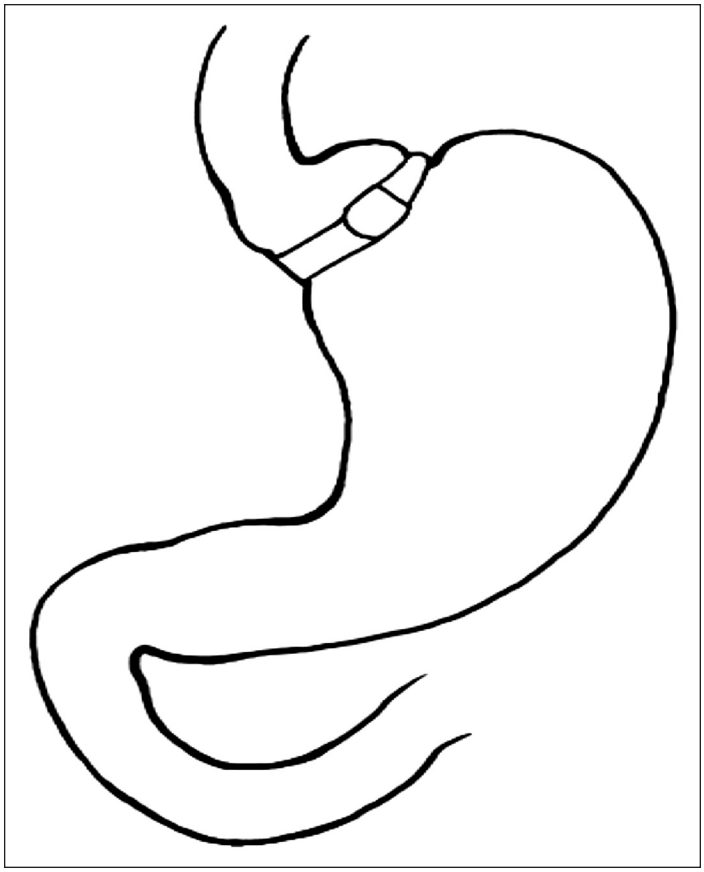

Figure 2. Adjustable gastric banding. Adapted with permission from e-SPEN.[8]

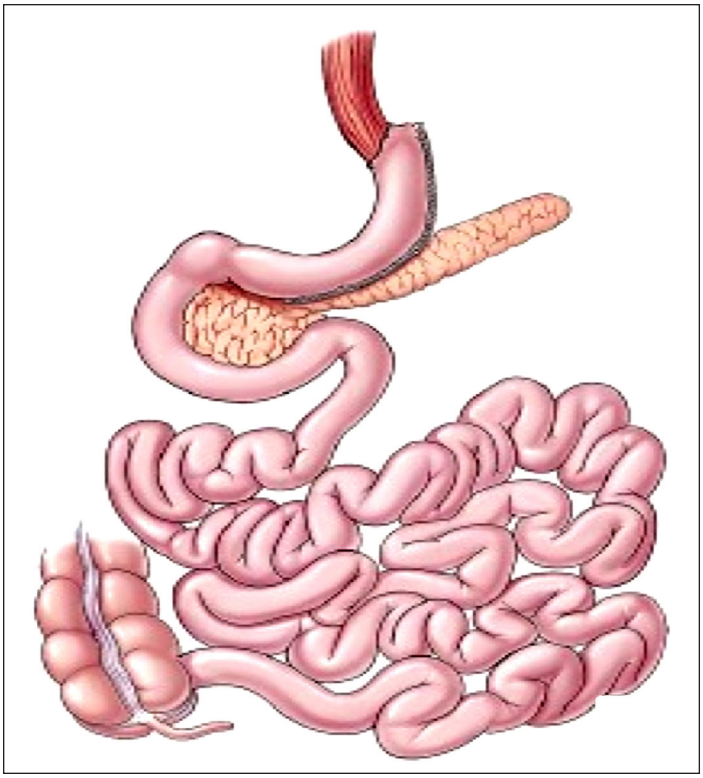

Figure 3. Sleeve gastrectomy. Adapted with permission from e-SPEN.[8]

of gastrointestinal absorptive area.[9] Today, RYGB is one of the most commonly performed bariatric surgical procedures (over 50% of all procedures in the United States in 2008) and is often referred to as the "gold standard technique."[10]

Mechanisms for Weight Reduction and Improvement of Diabetes by Bariatric Surgery

Although the traditional way of describing the effects of different procedures as restrictive, malabsorptive, or combined offers some explanation for the mechanisms by which different bariatric surgical procedures induce weight loss as well as improvement of diabetes, recent data suggest that this might be an oversimplification. For purely restrictive procedures, reduced capacity of intake of nutrients might be most important, although hormonal regulation of appetite by changes in leptin as well as ghrelin concentrations are believed to play a role.[11] In purely malabsorptive procedures, in particular BPD, the marked reduction in intestinal absorptive surface could be assumed to be the major mechanism for at least weight loss,[12] but in BPD-DS, the combination with a sleeve gastrectomy suggests that hormonal regulation as well as a restrictive component contribute as well.

For gastric bypass, the mechanisms seem to be even more complex, since neither restriction of nutrient intake through the gastroenteroanastomosis nor malabsorption due to the relatively short disconnected part of the small intestine offers a sole explanation. The anastomosis is typically wide enough to allow passage of excess amounts of nutrients, and it is well-known that the bypass of 120 cm of intestine is easily compensated for by adaptation over time. Suggested mechanisms behind the weight-reducing effects of RYGB include changes in eating habits with smaller and more frequent meals with a preference for vegetables, fruits, and meat in contrast to nutrients with high content of fat and sugar.[13] Also, in experimental models, energy expenditure has been demonstrated to be better preserved after gastric bypass compared to after-diet-induced weight loss of a similar degree.[14]

Regarding the antidiabetic effects of RYGB, the situation is even less well defined. Theoretically, an improvement of diabetes could be explained by a reduction of caloric intake, reduced amount of adipose tissue, changes in secretion of gastrointestinal hormones, or a combination of the three.[9] Interestingly, improvements in glycemic

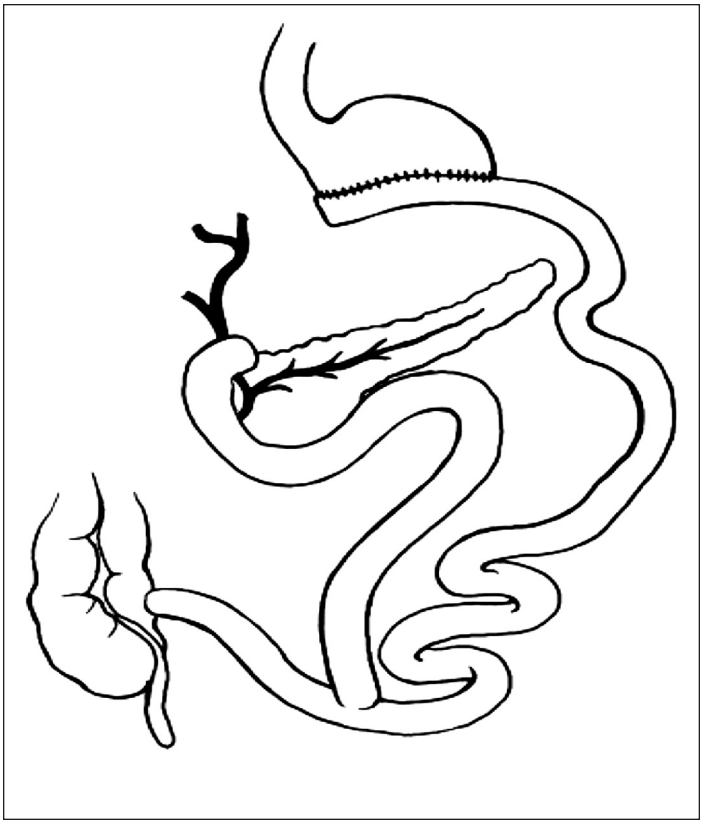

Figure 4. Biliopancreatic diversion. Adapted with permission from e-SPEN.[22]

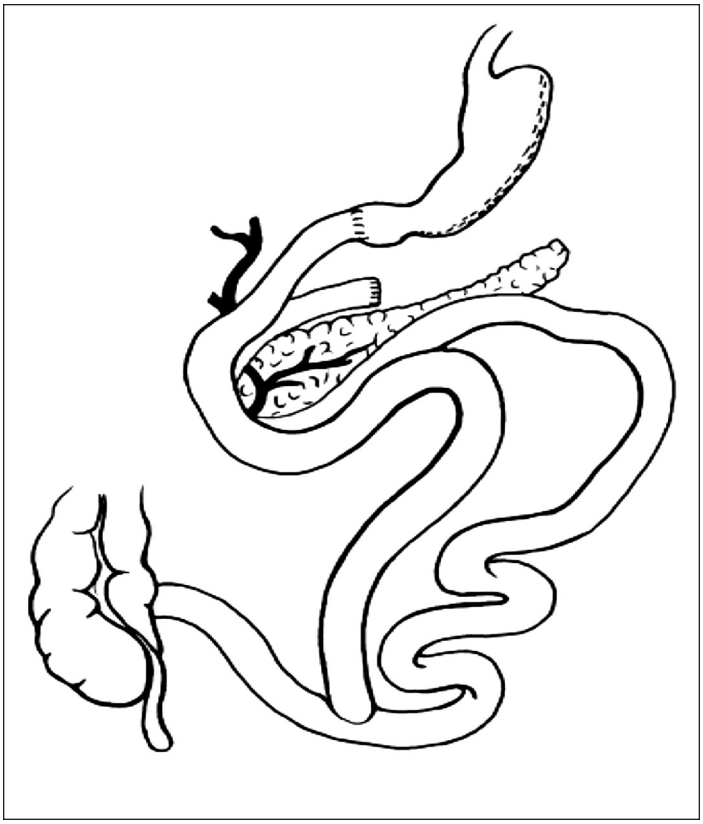

Figure 5. Biliopancreatic diversion with duodenal switch. Adapted with permission from e-SPEN.[22]

control or even resolution of diabetes are often achieved early, even before any substantial weight loss is present.[9] This suggests that a marked reduction of adipose tissue mass is not mandatory for improved glycemic control. Restriction to a very low calorie diet [(VLCD), 600–800 kcal/day] improves beta cell function and insulin sensitivity in just 1 week and could thus contribute to the effects seen early after RYGB.[15] Moreover, an important role also seems to be played by the altered anatomy with bypass of duodenum and proximal small intestine (foregut theory) and/or the delivery of nutrients to more distal parts of the small intestine with an increase of release of GLP-1 and peptide YY (hindgut theory).[16] The latter has been shown to be associated with earlier satiety, reduced caloric intake, as well as increased insulin release from pancreatic beta cells.[16]

Preoperative Very Low Calorie Diet

In order to get access to the stomach during bariatric surgery, the left lobe of the liver needs to be displaced by retractors. Patients with morbid obesity invariably suffer from a certain degree of hepatosteatosis or even nonalcoholic steatohepatitis[17] with increased liver volume, which might technically complicate the surgical procedure. Therefore, in many, if not most bariatric surgical centers,

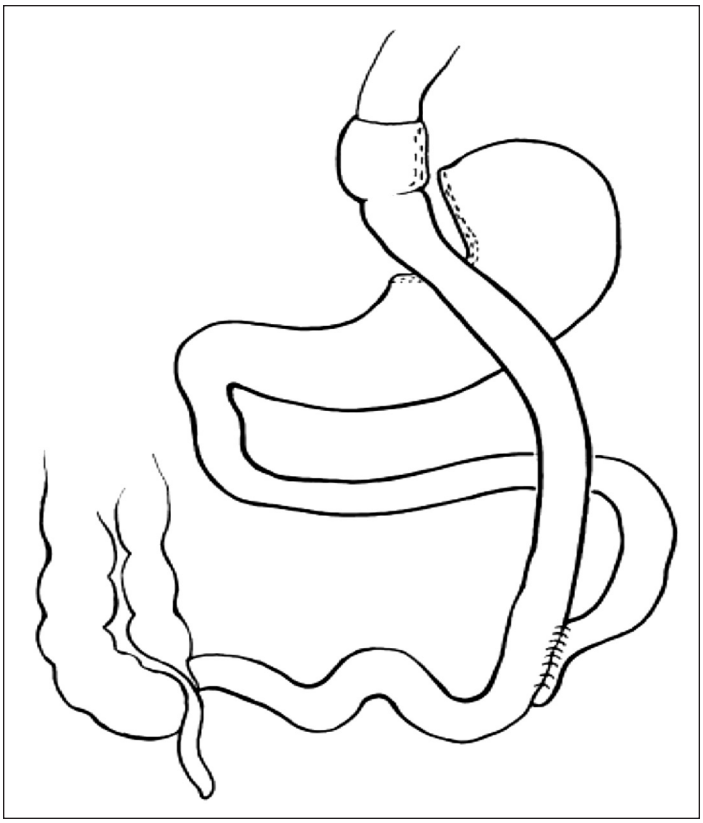

Figure 6. Roux-en-Y gastric bypass. Adapted with permission from e-SPEN.[2]

a preoperative period of VLCD is recommended for 2–3 weeks in order to reduce liver volume. This routine has been demonstrated to be associated with an approximate 15% reduction in liver volume,[18] which reduces both the surgeon´s perceived complexity with the procedure and postoperative complications.[19] Although not confirmed in controlled studies, the use of preoperative VLCD has also been suggested to be associated with improved postoperative weight reduction.[20] Since calorie restriction is known to increase insulin sensitivity, it is important to acknowledge the risk of hypoglycemia in patients on glucose-lowering drugs when preoperative VLCD is prescribed and to adjust medication accordingly, when needed.

Perioperative Antidiabetic Treatment

As stated earlier, there is an obvious need for careful monitoring of glucose control and adjustments of concomitant glucose-lowering therapy in patients with diabetes both before and after bariatric surgery. In patients on insulin or insulin secretagogues (sulphonylureas and meglitinides), combined restrictive and malabsorptive surgical techniques, such as RYGB, will induce rapid changes in insulin sensitivity and a risk of hypoglycemia. Moreover, in patients prescribed a preoperative VLCD period, any glucose-lowering drugs will most likely need to be reduced. Current guidelines do not offer detailed recommendations on antidiabetes drug adjustments before or after bariatric surgery, and the evidence base is scarce.[21] Until results from studies are available, the following recommendations have, in our experience, been shown to be applicable in most patients. It should be noted that the recommendations are based solely on our clinical experience and not from the result of any trials (see Summary of Recommendations for Adjustment of Antidiabetic Medication before and after Bariatric Surgery).

If possible, the preoperative glycemic control should be optimized by diet, physical activity, and antidiabetic drugs, although the effect of such efforts is not well explored in this group of patients. In a retrospective analysis of patients with T2DM undergoing bariatric surgery, preoperative hemoglobin A1c (HbA1c) >6.5% was shown to be associated with worse postoperative glycemic control and less weight loss compared with a group with lower HbA1c.[22] All patients on insulin or insulin secretagogues should be familiar with self-monitoring of blood glucose and how to adjust medication when needed. Also, ready access to consultation with a health professional (diabetes nurse, general physician, or diabetologist) is of great importance.

In patients prescribed VLCD before surgery, often during a period of 2 weeks, insulin secretagogues should be discontinued. Reintroducion is recommended by half of previous dose if fasting plasma glucose is repeatedly elevated above 180 mg/dl. It is proposed that patients on insulin should decrease doses of premixed or rapid-acting analog taken before meals by 50%. Doses of long-acting analogs or neutral protamine Hagedorn (NPH) insulin should be decreased by 30%. Patients on multiple doses of insulin should monitor glucose at least twice a day with a goal of plasma glucose 110–180 mg/dl. Further adjustments of the insulin doses should be considered if this level is not achieved. Patients are instructed how to reduce the insulin doses if hypoglycemia or repeated plasma glucose <90 mg/dl occur; i.e., decrease the insulin dose preceding the hypoglycemia by 50%. All other antidiabetic drugs are retained until surgery (metformin, GLP-1 analogs, inhibitors of dipeptidyl peptidase 4, glitazones, acarbose).

On the day of surgery, it is recommended not to give any antidiabetic medication, and that glucose is monitored and regulated by intravenous insulin infusion or repeated doses of rapid-acting insulin. If the postoperative course is uncomplicated, metformin can be reintroduced on day 1 after surgery. Long-acting or NPH insulin should be reintroduced at a dose corresponding to 50% of the earlier dose. Any other antidiabetic medication is discontinued.

During the subsequent period of weight loss, further improvement of glycemic control is expected, and the patient must be aware of the possible need for concomitant reduction of a remaining insulin dose in order to avoid hypoglycemic episodes. Similar levels of self-monitored plasma glucose as stated above (during preoperative VLCD-period) can be applied for dose reduction or withdrawal. Again, easy access to consultation with a diabetes nurse, diabetologist, or general physician is strongly recommended. Normalization of glycemic control and a state of remission of diabetes are seen in close to 80% of patients undergoing RYGB,[9] and thus, insulin can be tapered out in a majority of patients with T2DM.[16] However, diabetes is a chronic disease, and when weight stability is achieved—usually 12–18 months after surgery—some patients might relapse with increased glucose levels. It is not known whether metformin or lifestyle interventions, such as physical exercise, can prevent relapse in diabetes. However, because metformin is not associated with the risk for hypoglycemia or weight increase, this medication might be maintained or reintroduced in patients unless gastrointestinal side effects or contraindications such as renal failure are

present. Hence, there is a continuous need for follow-up with at least annual HbA1c. Likewise, many T2DM patients will have to continue lipid-lowering and anti-hypertensive medication and will need continuous follow-up as well.

Although much less frequent compared to T2DM, patients with type 1 diabetes and morbid obesity might also be in need of bariatric surgery. In type 1 diabetes, there is a continuous need for insulin for survival, and if this is not recognized by the surgeon or surgical staff, withdrawal could induce ketoacidosis in less than 24 h. Those patients should be monitored carefully, and the diabetologist should be consulted liberally. While meal-related insulin (rapid-acting) can often be reduced substantially, basal insulin (long-acting analogs or NPH insulin) should be reduced with great caution.

Summary of Recommendations for Adjustment of Antidiabetic Medication before and after Bariatric Surgery

General

- In patients on insulin or insulin secretagogues, good knowledge in home glucose monitoring to guide therapy adjustments is important
- Consultation with a health professional should be easily accessible
- Patients should recognize symptoms of and know how to treat hypoglycemia

During preoperative low calorie diet (approximately 2 weeks prior to surgery)

- Withdrawal of insulin secretagogues is recommended
- Reduce premix or rapid acting insulin by 50%
- Reduce NPH or long-acting analogs by 30%
- Monitor glucose at least twice a day
- Aim at plasma glucose 110–180 mg/dl. If glucose is repeatedly <90 mg/dl or hypoglycemia; further reduction of insulin (by 50%)

Postoperative (from day 1)

- Metformin is reintroduced
- Give 50% of preoperative NPH or long-acting analog insulin
- Readiness to treat stress hyperglycemia if complications occur
- Self-monitoring of glucose for further adjustments or withdrawal of insulin during weight loss in the later postoperative period

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